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09/628,225	07/28/2000	William W. Bachovchin	TUU-P01-006	3405

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EXAMINER
RUSSEL, JEFFREY E

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/628,225	Applicant(s) BACHOVCHIN ET AL.	
	Examiner Jeffrey E. Russel	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2001* .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27 and 29-67* is/are rejected.

7)☒ Claim(s) *28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *July 28, 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. Applicants indicate at the top of page 4 of the response filed November 30, 2001 that all claims are presented in the amendment section of the response regardless of whether or not the claims are being amended. However, there is no provision for this procedure in the amendment rule, and Applicants' proposed amendment format makes it difficult to identify and enter only those claims being amended. Any future responses should strictly follow the amendment procedures of 37 CFR 1.121.

37 CFR 1.121(b)(1)(iii) and (c)(1)(ii) require that the marked-up copies of the amendments be presented "on one or more pages separate from the amendment", which procedure was not followed in Applicants' response.

Claim 2 as set forth at page 4 of the response filed November 30, 2001 was not entered because it was not marked "(Amended)" as required by 37 CFR 1.121(c)(1)(i). Claim 12 as set forth at page 5 of the response was entered because it was marked "(Amended)", although the marked-up copy of the amended claim does not identify any changes to the claim language.

The response filed November 30, 2001 did not accurately mark all amendments to the claims as required by 37 CFR 1.121(c)(1). For example, the last line of the clean copy of amended claim 1 reads "at a", whereas the last line of the marked-up copy reads "having a". The last two lines of the clean copy of amended claim 4 read "which have", whereas the marked-up copy reads "having". In claims 8-10, "EC50" has been changed to "EC_{50}" without the changes having been identified in the marked-up copy. Throughout the claims, variable numbers have been subscripted (e.g., in claim 19, "R1", "R36", "R38", and "R40" have been changed to "R_1", "R_{36}", "R_{38}", and "R_{40}") without the changes being marked. The clean copy of amended claim 19 does not correspond with the marked up copy of amended claim 19 (note that at line 4 of the

clean copy of amended claim 19, "the" remains in the claim, and at lines 4-5 of the clean copy of amended claim 19, the phrase "as defined for A above" remains in the claim even though it was omitted without marking in the marked-up copy of amended claim 19). In the clean copy of amended claim 27, line 6, a single bond is present between the -CH and the NR_5 groups, whereas in the marked-up copy a double bond is present. In the clean copy of amended claim 27, the substituents at line 10 are repeated in a slightly different format than in the marked-up copy of amended claim 27, page 45, lines 1 and 2. In the clean copy of amended claim 27, line 12, "a thiocarbonyl," is present, in contrast to the marked-up copy of amended claim 27. In amended claim 28, the general formula was changed by insertion of an NH adjacent to the R_1 variable without the change having been marked. In the clean copy of amended claim 28, page 16, of the response, line 16, the term "heterocyclyl" is used, whereas in the marked-up copy of amended claim 28, "heterocycle" is used. In the clean copy of amended claim 28, page 16 of the amendment, line 17, there is no comma after "OH", whereas a comma is present after "OH" in the marked-up copy of amended claim 28. The clean copy of amended claim 31, page 18 of the amendment, lines 21-22, includes a definition of R'_7 which is not present in the marked-up copy of amended claim 31. At claim 31, page 19, line 1, the clean copy of the amended claim reads "an alkoxyl", whereas page 50, line 24, of the marked-up copy reads "and alkoxyl". Any future amendments to the claims should be carefully checked to ensure accurate marking of all amendments to the claims as required by 37 CFR 1.121.

2. With respect to the declaration signed by Inventor Bachavchin filed May 11, 2001, the examiner assumes that the inventor's post office address is the same as his residence address. If

this is incorrect, Applicant is required by 37 CFR 1.33(a) to provide a statement over applicant's signature providing a complete post office address.

The signed declaration referred to at page 52 of the response was not found attached to Applicants' submission.

3. The drawings are objected to because in the heading to Figure 3, "Pro(boro)pro" is misspelled. Correction is required.

Applicant is required to submit a proposed drawing correction in response to this Office action. Any proposal by Applicant for amendment of the drawings to cure defects must consist of two parts:

a) A separate letter to the Draftsperson in accordance with MPEP 608.02(r); and

b) A print or pen-and-ink sketch showing changes in red ink or with the changes otherwise highlighted in accordance with MPEP 608.02(v).

IMPORTANT NOTE: The filing of new formal drawings to correct the noted defect(s) may be deferred until the application is allowed by the examiner, but the print or pen-and-ink sketch with proposed corrections shown in red ink or with the changes otherwise highlighted is required in response to this Office action, and may not be deferred.

The corrected drawings for Figure 3 referred to at page 52 of the response was not found attached to Applicants' submission.

4. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 and/or 120 as follows:

The claim for priority inserted by the preliminary amendment filed July 28, 2000 is objected to because it does not indicate what type of priority is being claimed. For example, the

claim for priority does not use the "claims the benefit of" language which is indicative of a claim for priority under 35 U.S.C. 119(e), and does not use the "is a continuation of" language which is indicative of a claim for priority under 35 U.S.C. 120. The claim for priority inserted by the preliminary amendment filed July 28, 2000 is objected to because there is no copendency between either the U.S. Provisional Application or the PCT Application and the instant application. Note that the declaration indicates that a claim for priority under 35 U.S.C. 119 is intended, but both the U.S. Provisional Application and the PCT Application were filed more than one year prior to the filing date of the instant application. Finally, the claim for priority inserted by the preliminary amendment filed July 28, 2000 is objected to because it is not the first sentence of the specification. See MPEP 310.

Correction is required.

5. The disclosure is objected to because of the following informalities: At page 18, line 6, "halogenated" is misspelled. Appropriate correction is required.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-17, 19-22, 27, 42, 43, 54-56, 58-61, and 66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There is no original disclosure supporting the recitation that X_1 can be a hydroxyl as is recited in instant claims 15, 16, 27, 54, 55, and 66. Applicants have not indicated in their response where the original

disclosure of the invention supports the new claim language. There is no original disclosure for the cause of the glucose intolerance recited in instant claim 42. Applicants have not indicated in their response where the original disclosure of the invention supports the new claim language. The cause of the glucose intolerance recited in instant claim 42 seems inconsistent with the proposed mechanism of Applicants' invention. If the gene for a glucagon type peptide is deleted or disrupted, then presumably the glucagon type peptide is not being produced, and inhibiting the proteolysis of a glucagon type peptide which is not being produced would not be expected to have any in vivo effect.

7. Claims 27, 31-36, and 47-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 27 and 66 are indefinite because they define a variable R_1 which is not used in any of the chemical structures found in the claim. At claim 27, line 6, the second structural formula is incomplete because the double bond between the -CH and the NR_5 groups has been replaced with a single bond. Claim 31 is indefinite because it defines a variable R'_7 which is not used in any of the chemical structures found in the claim. Note that the variable R'_7 originally appeared in the definition of R_5, which definition was deleted in Applicants' amendment. To the extent that claims 47-54 and 63-67 depend upon claim 41, there is no antecedent basis in the claim for the phrase "the inhibitor". Claim 41 does not use the terminology "inhibitor". Claim 65 is indefinite because it defines a variable R_4 which is not used in any of the chemical structures found in the claim.

8. Claims 8, 16, 26, 28, 40, 42, 43, and 47-67 are objected to because of the following informalities: At claim 8, line 1, a space should be re-inserted between "claim" and "1". Claim

16 (page 8 of the response filed November 30, 2001, line 11) and claim 28 (page 16, line 19) should be revised to ensure the use of appropriate subscripts. At claim 26 (page 13, line 2) and claim 65 (page 29, line 7), "or" should be inserted before the last chemical structure in the line. At claim 28, line 1, one of the two occurrences of the claim number should be deleted. At claim 40, line 3, "with" should be deleted. Claim 57 does not end with a period. Appropriate correction is required.

9. Claims 22, 28, 44, 51, 61, and 67 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 22 and 61 recite that R_5 can be a halogenated lower alkyl, which is not a possibility embraced by the definition of R_5 in claims 15 and 54. Claim 28 does not further limit claim 15 because the inhibitor having the general formula recited in claim 28 does not comprise the 4-8 member heterocycle required by claim 15. Claim 44 is of identical scope as independent claim 38, which already requires the inhibition of DPIV-mediated proteolysis. Claim 45, to the extent that it depends upon claim 38, is of identical scope as claim 38, which already requires the inhibition of DPIV-mediated proteolysis. Claim 51 is broader in scope than claim 41 upon which it depends. Note that claim 41 requires a boronyl peptidomimetic, whereas claim 51 embraces any peptidomimetic. Claim 67 is broader in scope than claim 41 upon which it depends. Note that claim 41 requires a boronyl peptidomimetic, whereas claim 67 permits W to be groups other than $-BY_1Y_2$.

10. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

11. Claims 1-3, 5-13, 15, 16, 20, 21, 25, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application '309. The WO Patent Application '309 teaches administering DPIV inhibitors to treat human disease. The inhibitors are highly potent, with Ki values ranging into the nanomolar range or less, and are chemically stable. The DPIV inhibitors with the smallest Ki have the same structure as is set forth in Applicants' claims 15, 16, 20, 21, and 25. See, e.g., page 3, lines 10-21; page 4, lines 1-3; compounds 23, 38-40 and 97; and Table 9. Because the same active agents are being administered to the same animals according to the same method steps, inherently metabolism of GLP-1, glucose metabolism, insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, hyperlipoproteinemia, and peptide hormone metabolism will be modified to the same extent in the method of the WO Patent Application '309 as is claimed by Applicants. With respect to instant claims 8-10, in view of the similarity in structure and function between the DPIV inhibitor of the WO Patent Application '309 and Applicants' claimed DPIV inhibitor, the EC50's and Ki for the DPIV inhibitor of the WO Patent Application '309 will inherently be the same as is recited in instant claims 8-10. Sufficient evidence of similarity is deemed to be present between the DPIV inhibitor of the WO Patent Application '309 and the inhibitors recited in Applicants' claims to shift the burden to Applicants to provide evidence that their inhibitors are unobviously different than the DPIV inhibitors of the WO Patent Application '309.

12. Claims 1-3, 5-24, 26, 27, and 29-37 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application '259. The WO Patent Application '259 teaches inhibiting the enzymatic activity of DPIV in a mammal by administering a peptide compound. The peptides compounds are proteolyzed by DPIV in vivo until a C-terminal dipeptide portion

remains, which acts as an inhibitor of DPIV. The peptide compound is more stable in vivo than the C-terminal dipeptide portion. If the C-terminal dipeptide portion is chosen to be a dipeptide prolyl-boronic acid, then a potent and highly specific inhibitor having a Ki in the nanomolar range is ultimately released in vivo. Tetrapeptides comprising Ala-boroPro and Pro-boroPro as the C-terminal dipeptide portions are taught. As an alternative to the boroPro group, trifluoroalkyl ketone groups are taught. Administration can be oral. See, e.g., page 2, lines 15-32; page 3, line 1 - page 7, line 16; page 14, lines 10-12; page 14, line 34 - page 15, line 16; and page 21, line 15. Because the same active agents are being administered to the same animals according to the same method steps, inherently metabolism of GLP-1, glucose metabolism, insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, hyperlipoproteinemia, and peptide hormone metabolism will be modified to the same extent in the method of the WO Patent Application '259 as is claimed by Applicants. With respect to instant claims 8-11 and 33-35, in view of the similarity in structure and function between the DPIV inhibitors of the WO Patent Application '259 and Applicants' claimed DPIV inhibitors, the EC50's and Ki's for the DPIV inhibitors of the WO Patent Application '259 will inherently be the same as is recited in instant claims 8-11 and 33-35. Sufficient evidence of similarity is deemed to be present between the DPIV inhibitors of the WO Patent Application '259 and the inhibitors recited in Applicants' claims to shift the burden to Applicants to provide evidence that their inhibitors are unobviously different than the DPIV inhibitors of the WO Patent Application '259.

13. Claims 1-3, 5-13, 15, 16, 20, 21, and 25 are rejected under 35 U.S.C. 103(a) as being obvious over the Deacon et al article in view of the WO Patent Application '309. The Deacon et

al article teaches potentiating the insulinotropic effect of GLP-1 by administering a DPIV inhibitor, valine-pyrrolidide. Administration is in vivo to a pig, and results in reduced proteolysis of GLP-1, reduced blood glucose, and increased glucose tolerance. See, e.g., the Abstract; Figure 1; and page 768, column 1. The Deacon et al article does not disclose the use of DPIV inhibitors having a Ki as recited in instant claims 2 and 11, having an EC_{50} as recited in claims 8-10, having oral activity, or having the structure recited in instant claims 15, 16, 20, 21, and 25. Application of the WO Patent Application '309 is the same as in the above rejection of claims 1-3, 5-13, 15, 16, 20, 21, 25, and 29. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use the DPIV inhibitors of the WO Patent Application '309 in the method of the Deacon et al article because the DPIV inhibitors of the WO Patent Application '309 have the advantage of having a low Ki and of having chemical stability, which would permit the use of smaller dosages of the active agent, because the DPIV inhibitors of the WO Patent Application '309 are described as being generally useful as inhibitors of DPIV-mediated processes (see, e.g., the Abstract), and because the method of the Deacon et al article operates via a DPIV-mediated process. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to chose DPIV inhibitors from the WO Patent Application '309 for use in the method of the Deacon et al article so as to maximize their effectiveness in treating the intended disease and to minimize their unintended side effects, e.g., so as to minimize their EC_{50} for inhibiting glucose intolerance and to maximize their EC_{50} for causing immunosuppression.

14. Claims 1-3, 5-24, 26, 27, and 30-37 are rejected under 35 U.S.C. 103(a) as being obvious over the Deacon et al article in view of the WO Patent Application '259. The Deacon et al

article teaches potentiating the insulinotropic effect of GLP-1 by administering a DPIV inhibitor, valine-pyrrolidide. Administration is in vivo to a pig, and results in reduced proteolysis of GLP-1, reduced blood glucose, and increased glucose tolerance. See, e.g., the Abstract; Figure 1; and page 768, column 1. The Deacon et al article does not disclose the use of DPIV inhibitors having a Ki as recited in instant claims 2 and 11, having an EC_{50} as recited in claims 8-10, having oral activity, or having the structure recited in instant claims 15-24, 26, 27, and 31. Application of the WO Patent Application '259 is the same as in the above rejection of claims 1-3, 5-24, 26, 27, and 29-37. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use the DPIV inhibitors of the WO Patent Application '259 in the method of the Deacon et al article because the DPIV inhibitors of the WO Patent Application '259 have the advantage of having a low Ki and of having chemical stability, which would permit the use of smaller dosages of the active agent, because the DPIV inhibitors of the WO Patent Application '259 are described as being generally useful as inhibitors of DPIV-mediated processes (see, e.g., page 6, lines 4-10), and because the method of the Deacon et al article operates via a DPIV-mediated process. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to chose DPIV inhibitors from the WO Patent Application '259 for use in the method of the Deacon et al article so as to maximize their effectiveness in treating the intended disease and to minimize their unintended side effects, e.g., so as to minimize their EC_{50} for inhibiting glucose intolerance and to maximize their EC_{50} for causing immunosuppression.

15. Claims 38, 39, 44-49, 51, and 52 are rejected under 35 U.S.C. 103(a) as being obvious over the Deacon et al article in view of Efendic et al. The Deacon et al article teaches

potentiating the insulinotropic effect of GLP-1 by administering a DPIV inhibitor, valine-pyrrolidide. Administration is in vivo to a pig, and results in reduced proteolysis of GLP-1, reduced blood glucose, and increased glucose tolerance. See, e.g., the Abstract; Figure 1; and page 768, column 1. With respect to instant claims 47-49, in view of the similarity in structure and function between the DPIV inhibitor of the Deacon et al article and Applicants' claimed DPIV inhibitor, the EC50's for the DPIV inhibitor of the Deacon et al article will inherently be the same as is recited in instant claims 47-49. Sufficient evidence of similarity is deemed to be present between the DPIV inhibitor of the Deacon et al article and the inhibitors recited in Applicants' claims to shift the burden to Applicants to provide evidence that their inhibitors are unobviously different than the DPIV inhibitor of the Deacon et al article. The Deacon et al article teaches administration of GLP-1 in combination with a DPIV inhibitor in pigs, which were chosen because of their resemblance to humans in terms of gastrointestinal physiology (see page 764, column 2, second full paragraph), and teaches that this may be a viable approach to the management of diabetes (see the Abstract), but does not explicitly teach co-administering GLP-1 and a DPIV inhibitor to treat Type II diabetes. Efendic et al teach that diabetes is characterized by impaired glucose metabolism manifesting itself among other things by elevated blood glucose levels, i.e. that diabetic patients are glucose intolerant (see column 1, lines 19-21), and teach the administration of GLP-1 in order to treat type II diabetes (see, e.g., column 2, lines 37-49, and column 4, lines 47-67). It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to treat Type II diabetes using the combination of GLP-1 and a DPIV inhibitor taught by the Deacon et al article to treat Type II diabetes, because the Deacon et al article discloses that this may be a viable approach to the management of diabetes, because the

Deacon et al article's in vivo pig model is predictive of in vivo success in humans due to its resemblance to humans in terms of gastrointestinal physiology, and because Efendic et al confirm that GLP-1 is useful in the treatment of Type II diabetes.

16. Claims 4, 50, 54, 55, 59, 60, and 64 are rejected under 35 U.S.C. 103(a) as being obvious over the Deacon et al article in view of the WO Patent Application '309 as applied against instant claims 1-3, 5-13, 15, 16, 20, 21, and 25 above, and further in view of Efendic et al. The Deacon et al article teaches administration of GLP-1 in combination with a DPIV inhibitor in pigs, which were chosen because of their resemblance to humans in terms of gastrointestinal physiology (see page 764, column 2, second full paragraph), and teaches that this may be a viable approach to the management of diabetes (see the Abstract), but does not explicitly teach co-administering GLP-1 and a DPIV inhibitor to treat Type II diabetes. Efendic et al teach that diabetes is characterized by impaired glucose metabolism manifesting itself among other things by elevated blood glucose levels, i.e. that diabetic patients are glucose intolerant (see column 1, lines 19-21), and teach the administration of GLP-1 in order to treat type II diabetes (see, e.g., column 2, lines 37-49, and column 4, lines 47-67). It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to treat Type II diabetes using the combination of GLP-1 and a DPIV inhibitor suggested by the Deacon et al article as modified above by the WO Patent Application '309 to treat Type II diabetes, because the Deacon et al article discloses that this may be a viable approach to the management of diabetes, because the Deacon et al article's in vivo pig model is predictive of in vivo success in humans due to its resemblance to humans in terms of gastrointestinal physiology, and because Efendic et al confirm that GLP-1 is useful in the treatment of Type II diabetes.

17. Claims 4, 41, 50, 53-63, 65, and 66 are rejected under 35 U.S.C. 103(a) as being obvious over the Deacon et al article in view of the WO Patent Application '259 as applied against claims 1-3, 5-24, 26, 27, and 30-37 above, and further in view of Efendic et al. The Deacon et al article teaches administration of GLP-1 in combination with a DPIV inhibitor in pigs, which were chosen because of their resemblance to humans in terms of gastrointestinal physiology (see page 764, column 2, second full paragraph), and teaches that this may be a viable approach to the management of diabetes (see the Abstract), but does not explicitly teach co-administering GLP-1 and a DPIV inhibitor to treat Type II diabetes. Efendic et al teach that diabetes is characterized by impaired glucose metabolism manifesting itself among other things by elevated blood glucose levels, i.e. that diabetic patients are glucose intolerant (see column 1, lines 19-21), and teach the administration of GLP-1 in order to treat type II diabetes (see, e.g., column 2, lines 37-49, and column 4, lines 47-67). It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to treat Type II diabetes using the combination of GLP-1 and a DPIV inhibitor suggested by the Deacon et al article as modified above by the WO Patent Application '259 to treat Type II diabetes, because the Deacon et al article discloses that this may be a viable approach to the management of diabetes, because the Deacon et al article's in vivo pig model is predictive of in vivo success in humans due to its resemblance to humans in terms of gastrointestinal physiology, and because Efendic et al confirm that GLP-1 is useful in the treatment of Type II diabetes.

18. Claims 1-3, 5-13, 15-18, 20, 21, 24, 29-35, and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application '644. The WO Patent Application '644 teaches administering GLP-2 in combination with a DPP IV inhibitor such as Pro(boro)Pro in order to

promote the growth or small and/or large intestine tissue in a mammal. Treatment of diabetes mellitus is also mentioned. The DPP IV inhibitor prevents proteolysis of GLP-2. See, e.g., page 3, lines 20-32, page 7, lines 15-22; page 9, line 17 - page 10, line 4; page 17, line 32; and Example 6. Because the same active agents are being administered to the same animals according to the same method steps, inherently metabolism of GLP-1, glucose metabolism, insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, hyperlipoproteinemia, and peptide hormone metabolism will be modified to the same extent in the method of the WO Patent Application '644 as is claimed by Applicants. With respect to instant claims 2, 8-11, and 33-35, in view of the similarity in structure and function between the DPIV inhibitor of the WO Patent Application '644 and Applicants' claimed DPIV inhibitor, the EC50's and Ki for the DPIV inhibitor of the WO Patent Application '644 will inherently be the same as is recited in instant claims 2, 8-11, and 33-35. Sufficient evidence of similarity is deemed to be present between the DPIV inhibitor of the WO Patent Application '644 and the inhibitors recited in Applicants' claims to shift the burden to Applicants to provide evidence that their inhibitors are unobviously different than the DPIV inhibitors of the WO Patent Application '644.

19. Claims 4, 38-41, 44-52, 54-57, 59, 60, 63, and 66 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application '644. Application of the WO Patent Application '644 is the same as in the above rejection of claims 1-3, 5-13, 15-18, 20, 21, 24, 29-35, and 37. The WO Patent Application '644 discloses the treatment of diabetes mellitus, which inherently involves glucose intolerant subjects, but does not explicitly exemplify such treatment using GLP-2 in combination with a DPP IV inhibitor. It would have been obvious to one of ordinary skill in

the art at the time Applicants' invention was made to treat diabetes mellitus using a combination of GLP-2 and a DPP IV inhibitor because it is desirable to treat diabetes mellitus in patients and because the WO Patent Application '644 includes diabetes mellitus as a disease which can be treated with its GLP-2-containing compositions.

20. Claims 1-17, 20, 21, 29, 38, 39, 44-56, 59, and 60 are rejected under 35 U.S.C. 102(a) and (e) as being anticipated by Villhauer. Villhauer teaches treating non-insulin-dependent diabetes, i.e. Type II diabetes, and increasing glucose tolerance by administering a DPIV inhibitor having the same structure as Applicants' claims 15-17, 20, and 21. The inhibitors improve early insulin response to oral glucose challenges. Oral administration of the inhibitors is taught. See, e.g , the Abstract; column 9, lines 48-65; and column 10, lines 28-42. With respect to instant claims 2 and 8-11, in view of the similarity in structure and function between the DPIV inhibitor of Villhauer and Applicants' claimed DPIV inhibitor, the EC50's and Ki for the DPIV inhibitors of Villhauer will inherently be the same as is recited in instant claims 2 and 8-11. Sufficient evidence of similarity is deemed to be present between the DPIV inhibitors of Villhauer and the inhibitors recited in Applicants' claims to shift the burden to Applicants to provide evidence that their inhibitors are unobviously different than the DPIV inhibitors of Villhauer. With respect to instant claim 29, because the same active agents are being administered to the same animals according to the same method steps, inherently peptide hormone metabolism will be modified to the same extent in the method of Villhauer as is claimed by Applicants.

21. Claims 1-14, 29, 38-40, and 44-53 are rejected under 35 U.S.C. 102(b) as being anticipated by the German Patent 196 16 486. The German Patent '486 teaches using DP IV

inhibitors to inhibit degradation of gastric inhibitory peptides and glucagon-like peptides, which effect can be used to reduce blood sugar levels and to treat diabetes mellitus. Inhibitors include alanyl pyrolidide, isoleucyl thiazolidide, and N-valyl prolyl, O-benzoyl hydroxyl amine, and they can be administered orally. See, e.g., pages 1-2; page 10, line 21 - page 11, line 1; and page 11, line 15; of the attached translation. In view of the similarity in structure and function between the DPIV inhibitors of the German Patent '486 and Applicants' claimed DP IV inhibitors, the EC_{50} and K_i values for the DP IV inhibitors of the German Patent '486 will inherently be the same as those recited in the instant claims. Sufficient evidence of similarity is deemed to be present between the DP IV inhibitors of the German Patent '486 and the inhibitors recited in Applicants' claims to shift the burden to Applicants to provide evidence that their inhibitors are unobviously different than those of the German Patent '486.

22. Applicant's arguments filed November 30, 2001 have been fully considered but they are not persuasive.

Applicants did not correct the informalities in the claim for priority pointed out in the first Office action and repeated in paragraph 4 above. These informalities are not correctable by a substitute declaration or by Applicants' remarks. The informalities must be corrected by the insertion of an appropriate claim for priority as the first sentence of the specification.

Applicants did not respond to the remaining objection to the disclosure.

The objections to claims 22 and 28 under 37 CFR 1.75(c) are maintained because the change in claim dependency does not affect the analysis set forth in the objection.

The rejections based upon the Deacon et al article as the primary reference are maintained. The Deacon et al article remains prior art against the instant claims until Applicants

have submitted an appropriate claim for priority which antedates the Deacon et al article. See paragraph 4 above.

The anticipation rejections based upon the WO Patent Application '309 and the WO Patent Application '259 are maintained. Applicants' argument that accidental unwitting achievement of a claimed result can not constitute anticipation is not accepted because by definition, the doctrine of inherency requires the accidental or unwitting achievement of Applicants' claimed result. Applicants' analysis would mean that inherency rejections could never be made, a result which is not supported by the case law. Applicants' citation to Marshall is noted; however, Marshall does not represent the current state of the case law with respect to inherency and anticipation rejections. See MPEP 2112 and 2112.02 and especially Ex parte Novitski, 26 USPQ2d 1389, 1391 (BPAI 1993) cited therein. See also W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 1548, 220 USPQ 303, 309(Fed. Cir. 1983) (holding that it is irrelevant to the determination of anticipation whether those using the invention appreciated the results because "[w]ere that alone enough to prevent anticipation, it would be possible to obtain a patent for an old and unchanged process"), cert. denied, 469 U.S. 851 (1984) and Abbott Labs. v. Geneva Pharms., Inc., 182 F.3d 1315, 1319, 51 USPQ2d 1307, 1309(Fed. Cir. 1999) (stating that the "accidental and unwitting" cases are only applicable when the claimed invention is "anticipated by earlier work that produced no useful or appreciated result"), cert. denied, 528 U.S. 1078 (2000).

The WO Patent Application '309 and the WO Patent Application '259 are not applied by themselves against instant claims 38-67. These claims require the treatment of a glucose

intolerant animal, and there is no teaching or suggestion in the WO Patent Application '309 or in the WO Patent Application '259 to administer its protease inhibitors to this subset of animals.

The anticipation rejection based upon the WO Patent Application '644 is maintained. The WO Patent Application '644 remains prior art against the instant claims until Applicants have submitted an appropriate claim for priority which antedates the WO Patent Application '644. See paragraph 4 above. If Applicants submit an appropriate claim for priority which antedates the WO Patent Application '644, the examiner will substitute its equivalent, U.S. Patent No. 5,952,301, in its place, and the U.S. patent will be available as prior art under 35 U.S.C. 102(e).

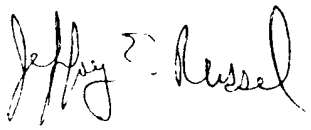
The anticipation rejection based upon Villhauer is maintained. Exhibit A was not found attached to Applicants' response, so the examiner has not considered the article and has not considered whether the Cheng-Prusoff equation is predictive of the enzyme-inhibitor systems at issue in Villhauer. Assuming that Applicants' summary of the equation is correct, that K_{id} (sic - K_i?) values will always be less than or equal to IC_{50} values, and assuming that an IC_{50} value of 3 nM is representative of the inhibitors of Villhauer, then Applicants' currently claimed K_i values, i.e. less than 1 nM, are consistent with the IC_{50} values of Villhauer, i.e. the former are less than or equal to the latter. It is not seen how this argument distinguishes over Villhauer. Further, it is not seen how compounds which have the same structures as those recited in Applicants' dependent claims can fail to meet the K_i requirements of the independent claim. In any event, if Applicants assert that the K_i values of Villhauer's inhibitors do not meet the numerical ranges recited in certain of Applicants' claims, it is best to test Villhauer's inhibitors directly rather than trying to infer their K_i values from some theoretical equation whose assumptions may or may not

correspond with the enzyme-inhibitor system of Villhauer. It is also noted that the newly added claims do not contain a K_i limitation, and that Villhauer teaches the treatment of diabetes mellitus and of impaired glucose tolerance. Accordingly, it is not seen how the newly added claims distinguish over Villhauer.

23. Claim 28 is objected to, but would be allowable if rewritten to overcome the claim objections set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. Claim 67 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, and the claim objections set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. The prior art of record does not teach or suggest that compounds having the structures recited in instant claims 28 and 67 have DPIV inhibitory activity, and therefore there would be no motivation to administer such compounds in vivo in order to treat DPIV-mediated conditions.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Christopher Low can be reached at (703) 308-2923. The fax number for Art Unit 1653 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.



Jeffrey E. Russel
Primary Patent Examiner
Art Unit 1653

JRussel
January 17, 2002